Pembrolizumab combination as a potentially transformative treatment for HER2-positive gastric cancer

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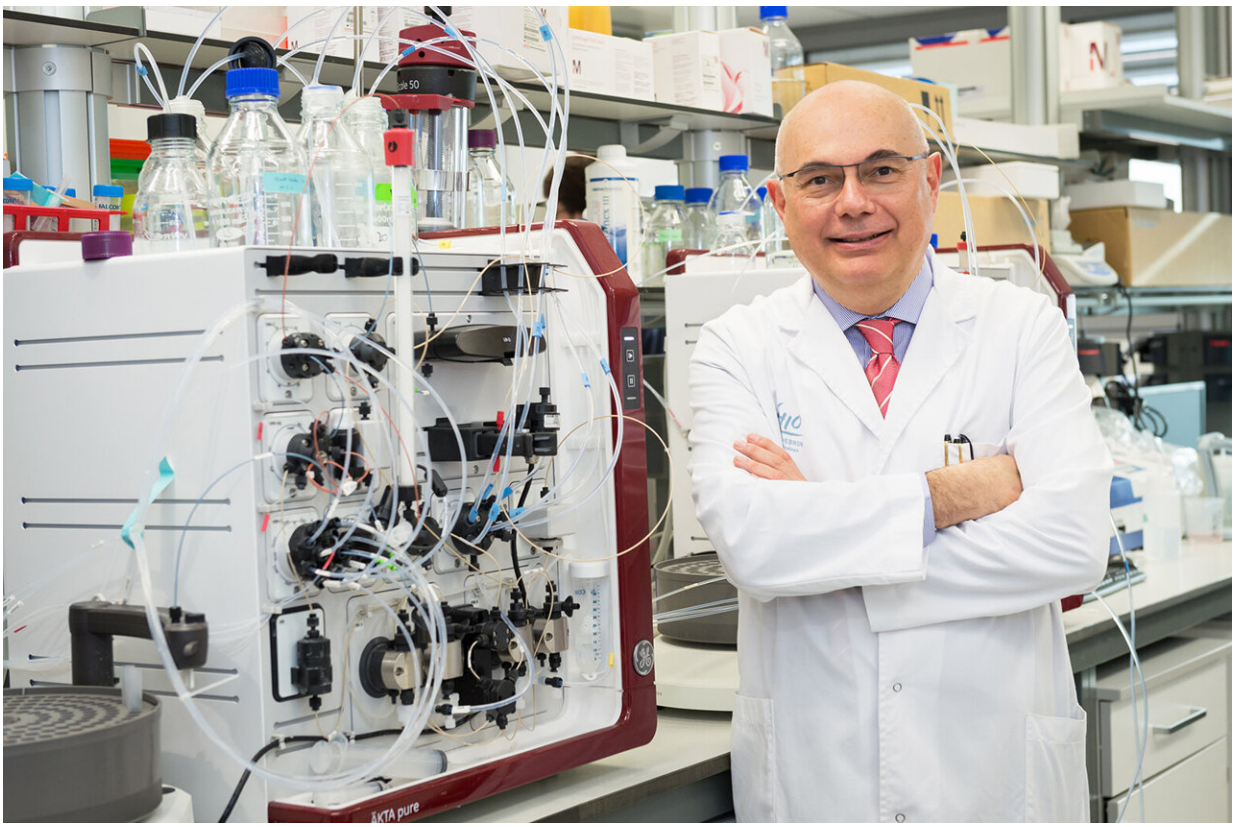

Josep Tabernero, Director, Vall d'Hebron Institute of Oncology (VHIO), Head, Medical Oncology Department, Vall d'Hebron University Hospital (HUVH), Barcelona, Spain. Credit: Vall d'Hebron Institute of Oncology

Initial findings of the phase III KEYNOTE-811 trial of pembrolizumab plus trastuzumab and chemotherapy—first presented at ASCO 2021—have led to the subsequent FDA approval of this combination for the first-line treatment of patients with HER2+ gastric cancer.

Published in *Nature*, results of the interim analysis show that this novel triplet combination markedly reduces tumor size, induces a complete response in some patients, and significantly improves objective response.

This study, upon completion, could lead to a paradigm shift in the treatment of patients with locally advanced unresectable or metastatic HER2+ gastric or gastroesophageal junction adenocarcinoma.

According to a recent report, gastric cancer is responsible for over one million new cases worldwide in 2020, with an increasing incidence among young adults (aged under 50 years). Ranking fifth for cancer incidence and fourth for cancer mortality, with an estimated 769,000 deaths globally in 2020, this tumor type represents a major healthcare challenge.

Approximately 20% of advanced gastric and gastroesophageal junction cancers have overexpression or amplification of human epidermal growth factor receptor 2 (HER2), which associates with a poor prognosis and increased disease recurrence and mortality. For over a decade, the combination of anti-HER2 antibody trastuzumab and chemotherapy has constituted the standard first-line treatment for patients with HER2-positive disease.

KEYNOTE-811: Ringing in IO-based therapy for HER2+ gastric cancer

Previous phase II studies combining PD-1 antibody pembrolizumab with

trastuzumab and chemotherapy have shown increased clinical efficacy and a manageable safety profile in patients with HER2-positive advanced gastric or gastroesophageal junction adenocarcinoma.

Building on these encouraging results, the randomized, double-blind, global phase III KEYNOTE-811 trial, led by Yelena Y. Janjigian, Chief of the Gastrointestinal Oncology Service, Memorial Sloan Kettering Cancer Center (MSKCC, New York, U.S.), was designed to further assess this novel triplet combination in this patient population.

Publishing today in*Nature* , the KEYNOTE-811 investigators, including Vall d'Hebron Institute of Oncology (VHIO)'s Director, Josep Tabernero, report results from the interim analysis of the first 264 patients who were randomly assigned 1:1 to receive pembrolizumab or placebo in combination with trastuzumab and chemotherapy.

Data show that the objective response rate was 74.4% in the pembrolizumab arm and 51.9% in the placebo arm, which represents a 22.7% improvement versus trastuzumab and chemotherapy, and supports preclinical data suggesting a possible synergy between dual HER2 and PD1 blockade.

"This study is the first to show the efficacy of a PD-1 immune checkpoint inhibitor in this particular patient population. Not only did the combination of pembrolizumab, trastuzumab, and chemotherapy significantly improve objective response rate, it also markedly reduced tumor size and induced complete responses in some patients," said co-author Josep Tabernero, head of the Medical Oncology Department, Vall d'Hebron University Hospital (HUVH, Barcelona, Spain).

"While these results are promising, the completion of this clinical trial will confirm whether our data translates in improved progression-free survival as well as overall survival," he added.

More information: Yelena Y. Janjigian et al, The KEYNOTE-811 trial of dual PD-1 and HER2 blockade in HER2-positive gastric cancer, *Nature* (2021). DOI: 10.1038/s41586-021-04161-3